Claims

We claim:

1. A calcium channel blocker compound having at least one of the following characteristics:

a. the compound is metabolized both by CYP450 and by a non-oxidative metabolic enzyme or system of enzymes;

b. the compound has a short (up to four (4) hours) non-oxidative metabolic half-life;

c. the compound contains a hydrolysable bond that can be cleaved non-oxidatively by hydrolytic enzymes;

d. the primary metabolites of the compound result from the non-oxidative metabolism of the compound;

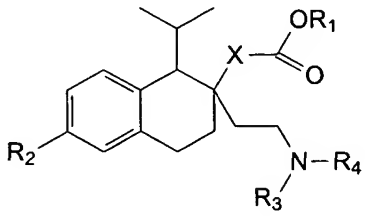
e. the primary metabolites are soluble in water at physiological pH;

f. the primary metabolites have negligible inhibitory activity at the IK_R (HERG) channel at normal therapeutic concentration of the parent drug in plasma;

g. the compound, as well as the metabolites thereof, does not cause metabolic DDI when co-administered with other drugs; and

h. the compound, as well as metabolites thereof, does not elevate LFT values when administered alone.

2. The compound, according to claim 1, having the following structure:



wherein:

X = a bond, $(CH_2)_n$, O, S, or $O(CH_2)_n$,

wherein n = 1-6;

R_1 = C_{1-6} alkyl, optionally substituted with OH or NH_2;

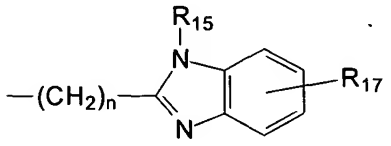
R_2 = F or $COOR_5$,

wherein R_5 is C_{1-6} alkyl, optionally substituted with OH or NH_2;

R_3 = CH_3 or $(CH_2)_n$ - $COOR_6$,

wherein n = 1-6 and R_6 is C_{1-6} alkyl, optionally substituted with OH or NH_2;

R_4 = $(CH_2)_n$ - COR_7R_8, -$(CH_2)_n$ -$R_{10}R_{11}$ or



R_7 = O, NH, or NR_9,

R_8 = optionally substituted aryl or heterocycle,

R_9 = C_{1-6} alkyl,

R_{10} = O, S, SO, SO_2, NH, NR_{12} or $N(CH_2)_m$ $COOR_{13}$,

R_{11} = aryl or heterocyclyl optionally substituted with $(CH_2)_n$ $COOR_{14}$,

R_{12} = C_{1-6} alkyl, optionally substituted with OH or NH_2,

R_{13} = C_{1-6} alkyl, optionally substituted with OH or NH_2,

R_{14} = C_{1-6} alkyl, optionally substituted with OH or NH_2,

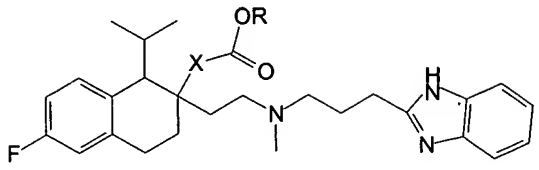
R_{15} = $(CH_2)_n$ $COOR_{16}$,

R_{16} = C_{1-6} alkyl, optionally substituted with OH or NH_2,

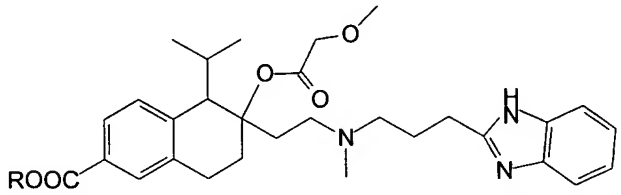
R_{17} = not present or $COOR_{18}$ wherein R_{18} is C_{1-6} alkyl, optionally substituted with OH or NH_2, and

wherein n = 1-6.

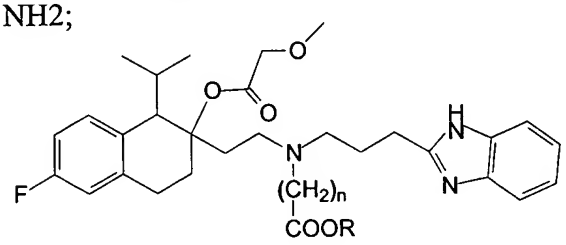
3. The compound, according to claim 2, having a formula selected from the group consisting of:



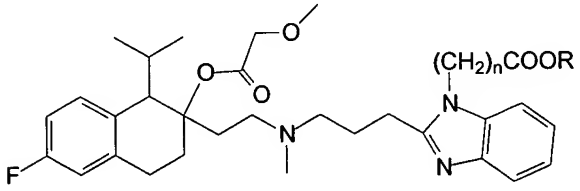
X = bond, CH_2, or OCH_2
R = lower alkyl optionally substituted OH or NH_2;



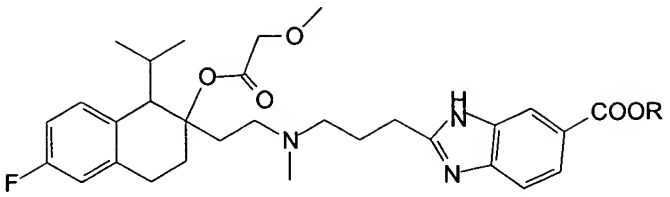
R = lower alkyl optionally substituted by OH or NH2;



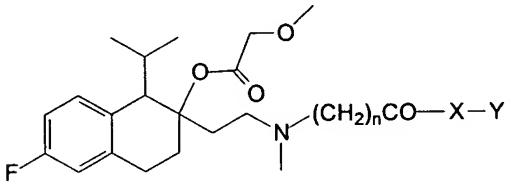
n = 1 to 3
R = lower alkyl optionally substituted by OH or NH_2;



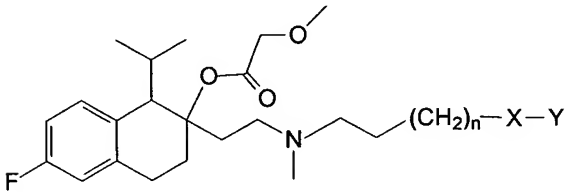
n = 1 to 3
R = lower alkyl optionally substituted by OH or NH_2;



R = lower alkyl optionally substituted by OH or NH_2;

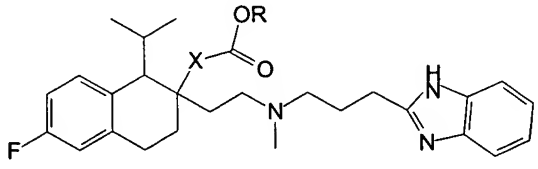


n = 1 to 3
X = O, NH, NR where R is lower alkyl
Y = optionally substituted aryl or heterocyclyl; and



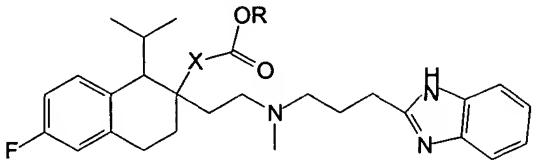
n = 0 to 2
X = O, S, SO, SO_2, NH NR or $N(CH_2)_mCOOH$ where m is 0 or 2
Y = aryl or heterocyclyl substituted with $(CH_2)_mCOOH$ where m is 0 to 2.

4. The compound, according to claim 3, having the following structure:



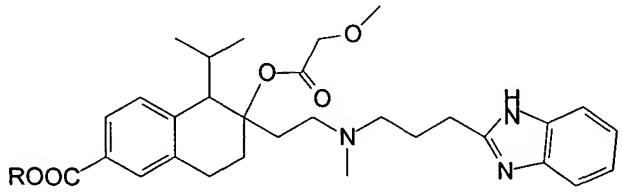
X = bond, CH_2, or OCH_2
R = lower alkyl optionally substituted OH or NH_2.

5. The compound, according to claim 3, having the following structure:



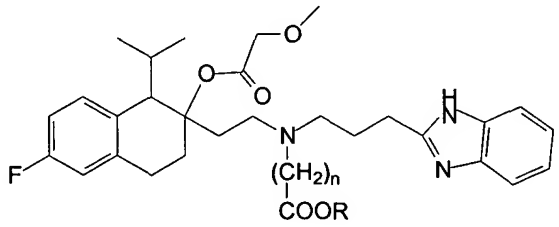
X = bond, CH_2, or OCH_2
R = lower alkyl optionally substituted OH or NH_2.

6. The compound, according to claim 3, having the following structure:



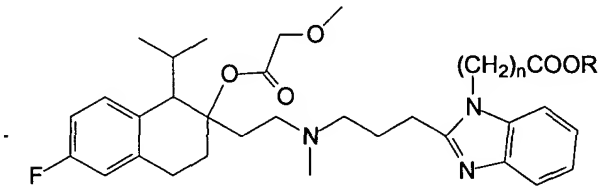
R = lower alkyl optionally substituted by OH or NH_2.

7. The compound, according to claim 3, having the following structure:



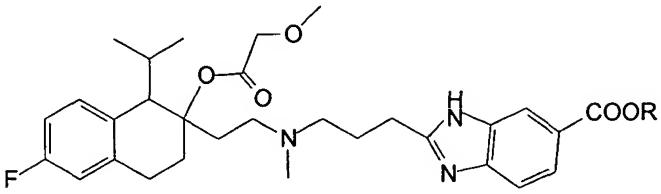
n = 1 to 3
R = lower alkyl optionally substituted by OH or NH_2.

8. The compound, according to claim 3, having the following structure:



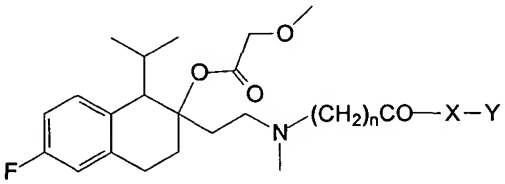
n = 1 to 3
R = lower alkyl optionally substituted by OH or NH_2.

9. The compound, according to claim 3, having the following structure:



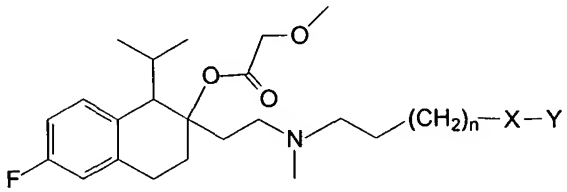
R = lower alkyl optionally substituted by OH or NH_2.

10. The compound, according to claim 3, having the following structure:



n = 1 to 3
X = O, NH, NR where R is lower alkyl
Y = optionally substituted aryl or heterocyclyl.

11. The compound, according to claim 3, having the following structure:



n = 0 to 2
X = O, S, SO, SO_2, NH NR or $N(CH_2)_mCOOH$ where m is 0 or 2
Y = aryl or heterocyclyl substituted with $(CH_2)_mCOOH$ where m is 0 to 2.

12. A pharmaceutical composition comprising a calcium channel blocker compound having at least one of the following characteristics:

a. the compound is metabolized both by CYP450 and by a non-oxidative metabolic enzyme or system of enzymes;

b. the compound has a short (up to four (4) hours) non-oxidative metabolic half-life;

c. the compound contains a hydrolysable bond that can be cleaved non-oxidatively by hydrolytic enzymes;

d. the primary metabolites of the compound result from the non-oxidative metabolism of the compound;

e. the primary metabolites are soluble in water at physiological pH;

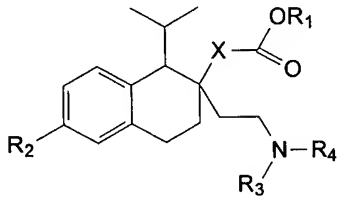
f. the primary metabolites have negligible inhibitory activity at the IK_R (HERG) channel at normal therapeutic concentration of the parent drug in plasma;

g. the compound, as well as the metabolites thereof, does not cause metabolic DDI when co-administered with other drugs; and

h. the compound, as well as metabolites thereof, does not elevate LFT values when administered alone;

wherein said composition further comprises a pharmaceutical carrier.

13. The pharmaceutical composition, according to claim 12, wherein said compound has the following structure:



wherein:

X = a bond, $(CH_2)_n$, O, S, or $O(CH_2)_n$,

wherein n = 1-6;

R_1 = C_{1-6} alkyl, optionally substituted with OH or NH_2;

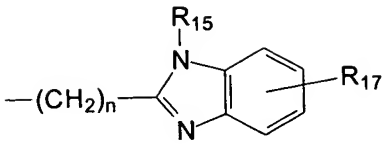
R_2 = F or $COOR_5$,

wherein R_5 is C_{1-6} alkyl, optionally substituted with OH or NH_2;

R_3 = CH_3 or $(CH_2)_n$ - $COOR_6$,

wherein n = 1-6 and R_6 is C_{1-6} alkyl, optionally substituted with OH or NH_2;

R_4 = $(CH_2)_n$ - COR_7R_8, $-(CH_2)_n-R_{10}R_{11}$ or



R_7 = O, NH, or NR_9,

R_8 = optionally substituted aryl or heterocycle,

R_9 = C_{1-6} alkyl,

R_{10} = O, S, SO, SO_2, NH, NR_{12} or $N(CH_2)_m$ $COOR_{13}$,

R_{11} = aryl or heterocyclyl optionally substituted with $(CH_2)_n$ $COOR_{14}$,

R_{12} = C_{1-6} alkyl, optionally substituted with OH or NH_2,

R_{13} = C_{1-6} alkyl, optionally substituted with OH or NH_2,

R_{14} = C_{1-6} alkyl, optionally substituted with OH or NH_2,

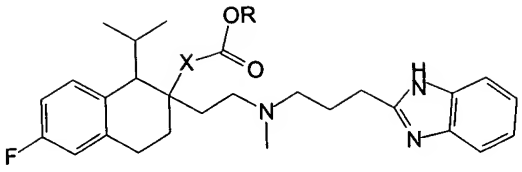
R_{15} = $(CH_2)_n$ $COOR_{16}$,

R_{16} = C_{1-6} alkyl, optionally substituted with OH or NH_2,

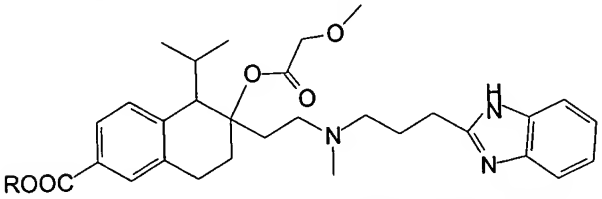
R_{17} = not present or $COOR_{18}$ wherein R_{18} is C_{1-6} alkyl, optionally substituted with OH or NH_2, and

wherein n = 1-6.

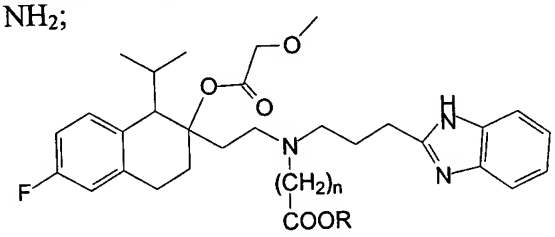
14. The composition, according to claim 13, comprising a compound having a formula selected from the group consisting of:



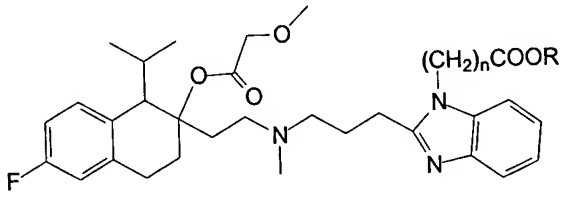
X = bond, CH_2, or OCH_2
R = lower alkyl optionally substituted OH or NH_2;



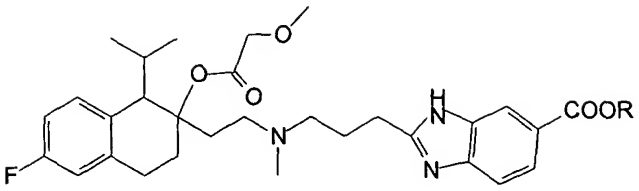
R = lower alkyl optionally substituted by OH or NH_2;



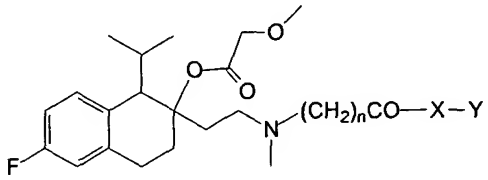
n = 1 to 3
R = lower alkyl optionally substituted by OH or NH_2;



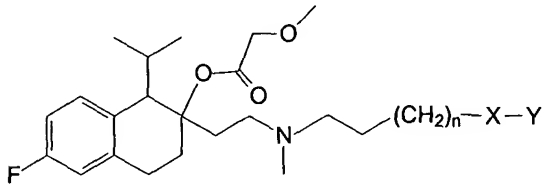
n = 1 to 3
R = lower alkyl optionally substituted by OH or NH_2;



R = lower alkyl optionally substituted by OH or NH_2;

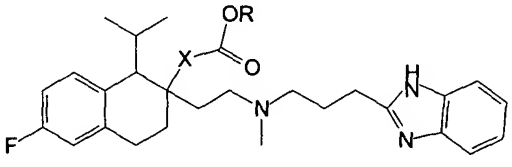


n = 1 to 3
X = O, NH, NR where R is lower alkyl
Y = optionally substituted aryl or heterocyclyl; and



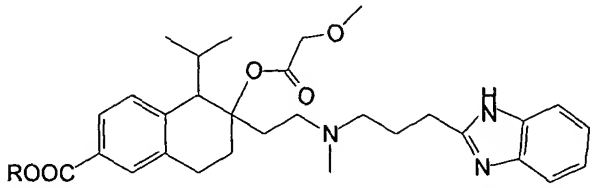
n = 0 to 2
X = O, S, SO, SO_2, NH NR or $N(CH_2)_mCOOH$ where m is 0 or 2
Y = aryl or heterocyclyl substituted with $(CH_2)_mCOOH$ where m is 0 to 2.

15. The composition, according to claim 14, comprising a compound having the following structure:



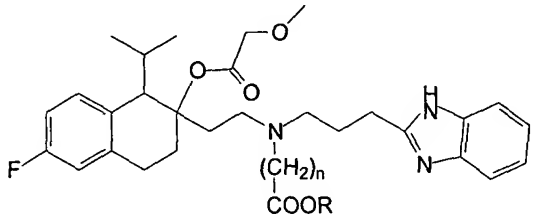
X = bond, CH_2, or OCH_2
R = lower alkyl optionally substituted OH or NH_2.

16. The composition, according to claim 14, having the following structure:



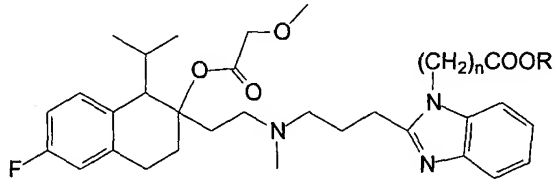
R = lower alkyl optionally substituted by OH or NH_2.

17. The composition, according to claim 14, having the following structure:



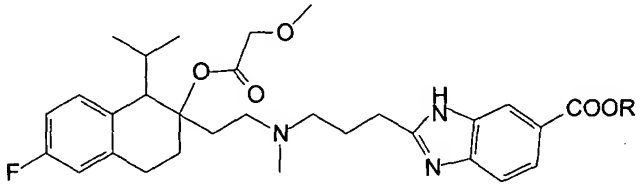
n = 1 to 3
R = lower alkyl optionally substituted by OH or NH_2.

18. The composition, according to claim 14, having the following structure:



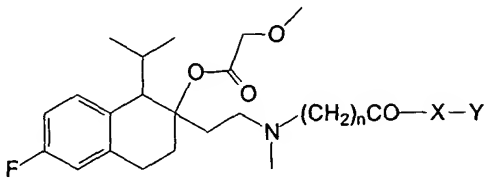
n = 1 to 3
R = lower alkyl optionally substituted by OH or NH_2.

19. The composition, according to claim 14, having the following structure:



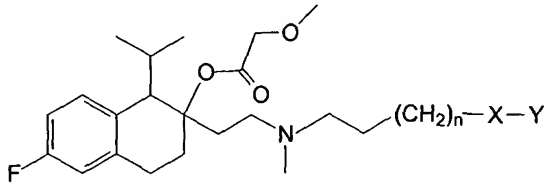
R = lower alkyl optionally substituted by OH or NH_2.

20. The composition, according to claim 14, having the following structure:



n = 1 to 3
X = O, NH, NR where R is lower alkyl
Y = optionally substituted aryl or heterocyclyl.

21. The composition, according to claim 14, having the following structure:



n = 0 to 2
X = O, S, SO, SO_2, NH NR or $N(CH_2)_mCOOH$ where m is 0 or 2
Y = aryl or heterocyclyl substituted with $(CH_2)_mCOOH$ where m is 0 to 2.

22. A method for blocking a calcium channel in a patient in need of such treatment wherein said method comprises administering to said patient a calcium channel blocking compound having at least one of the following characteristics:

a. the compound is metabolized both by CYP450 and by a non-oxidative metabolic enzyme or system of enzymes;

b. the compound has a short (up to four (4) hours) non-oxidative metabolic half-life;

c. the compound contains a hydrolysable bond that can be cleaved non-oxidatively by hydrolytic enzymes;

d. the primary metabolites of the compound result from the non-oxidative metabolism of the compound;

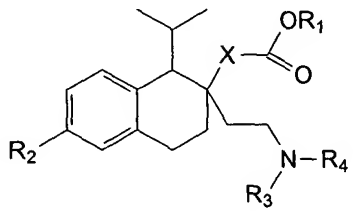
e. the primary metabolites are soluble in water at physiological pH;

f. the primary metabolites have negligible inhibitory activity at the IK_R (HERG) channel at normal therapeutic concentration of the parent drug in plasma;

g. the compound, as well as the metabolites thereof, does not cause metabolic DDI when co-administered with other drugs; and

h. the compound, as well as metabolites thereof, does not elevate LFT values when administered alone.

23. The method, according to claim 22, wherein said compound has the following structure:



wherein:

X = a bond, $(CH_2)_n$, O, S, or $O(CH_2)_n$,

wherein n = 1-6;

R_1 = C_{1-6} alkyl, optionally substituted with OH or NH_2;

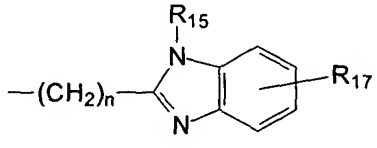
R_2 = F or $COOR_5$,

wherein R_5 is C_{1-6} alkyl, optionally substituted with OH or NH_2;

R_3 = CH_3 or $(CH_2)_n$ - $COOR_6$,

wherein n = 1-6 and R_6 is C_{1-6} alkyl, optionally substituted with OH or NH_2;

R_4 = $(CH_2)_n$ - COR_7R_8, $-(CH_2)_n-R_{10}R_{11}$ or



R_7 = O, NH, or NR_9,

R_8 = optionally substituted aryl or heterocycle,

R_9 = C_{1-6} alkyl,

R_{10} = O, S, SO, SO_2, NH, NR_{12} or $N(CH_2)_m$ $COOR_{13}$,

R_{11} = aryl or heterocyclyl optionally substituted with $(CH_2)_n$ $COOR_{14}$,

R_{12} = C_{1-6} alkyl, optionally substituted with OH or NH_2,

R_{13} = C_{1-6} alkyl, optionally substituted with OH or NH_2,

R_{14} = C_{1-6} alkyl, optionally substituted with OH or NH_2,

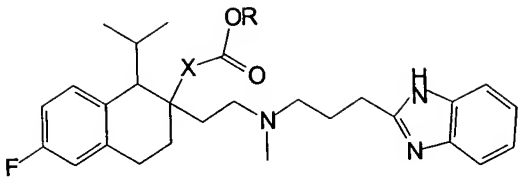
R_{15} = $(CH_2)_n$ $COOR_{16}$,

R_{16} = C_{1-6} alkyl, optionally substituted with OH or NH_2,

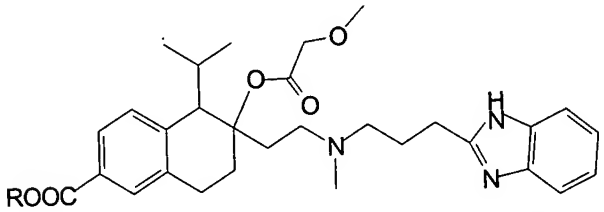
R_{17} = not present or $COOR_{18}$ wherein R_{18} is C_{1-6} alkyl, optionally substituted with OH or NH_2, and

wherein n = 1-6.

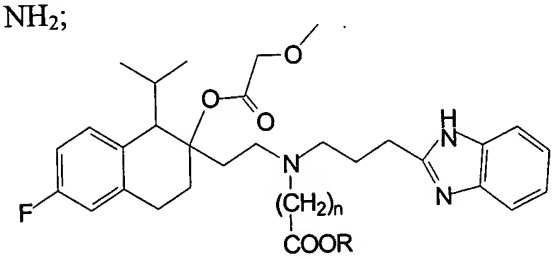
24. The method, according to claim 23, wherein said compound has a formula selected from the group consisting of:



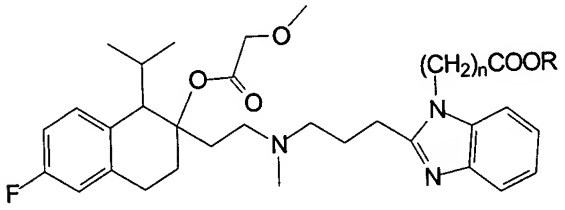
X = bond, CH_2, or OCH_2
R = lower alkyl optionally substituted OH or NH_2;



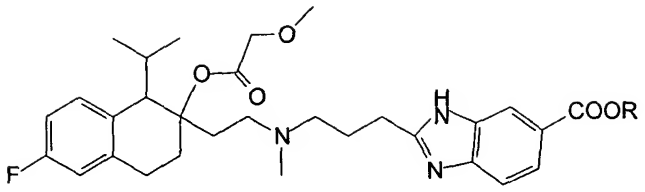
R = lower alkyl optionally substituted by OH or NH_2;



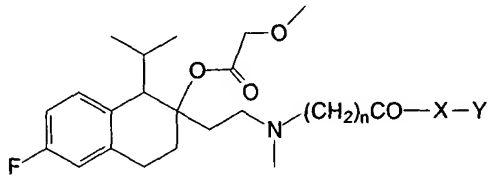
n = 1 to 3
R = lower alkyl optionally substituted by OH or NH_2;



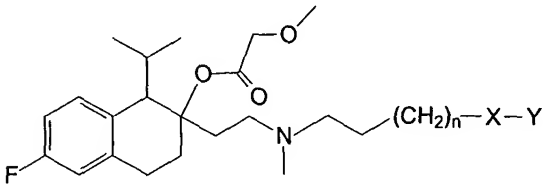
n = 1 to 3
R = lower alkyl optionally substituted by OH or NH_2;



R = lower alkyl optionally substituted by OH or NH_2;

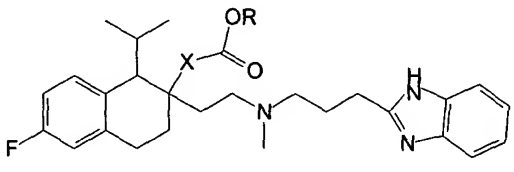


n = 1 to 3
X = O, NH, NR where R is lower alkyl
Y = optionally substituted aryl or heterocyclyl; and



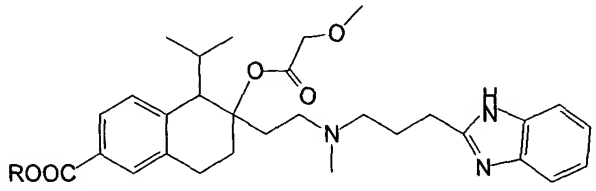
n = 0 to 2
X = O, S, SO, SO_2, NH NR or $N(CH_2)_mCOOH$ where m is 0 or 2
Y = aryl or heterocyclyl substituted with $(CH_2)_mCOOH$ where m is 0 to 2.

25. The method, according to claim 24, wherein said compound has the following structure:



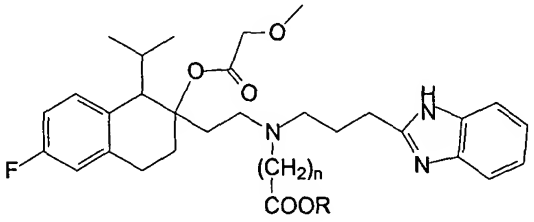
X = bond, CH_2, or OCH_2
R = lower alkyl optionally substituted OH or NH_2.

26. The method, according to claim 24, wherein said compound has the following structure:



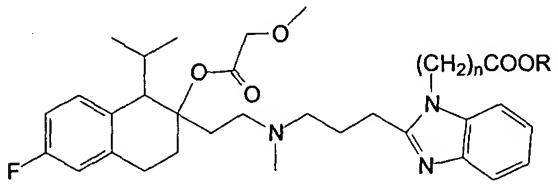
R = lower alkyl optionally substituted by OH or NH_2.

27. The method, according to claim 24, wherein said compound has the following structure:



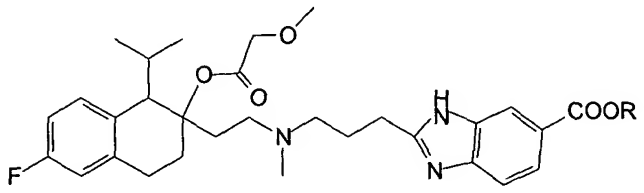
n = 1 to 3
R = lower alkyl optionally substituted by OH or NH_2.

28. The method, according to claim 24, wherein said compound has the following structure:



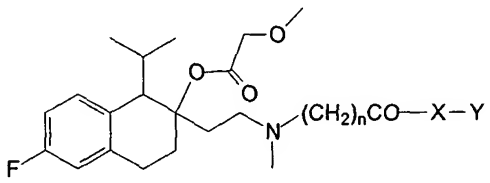
n = 1 to 3
R = lower alkyl optionally substituted by OH or NH_2.

29. The method, according to claim 24, wherein said compound has the following structure:



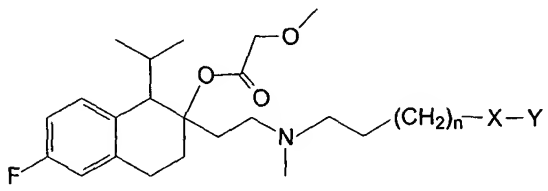
R = lower alkyl optionally substituted by OH or NH_2.

30. The method, according to claim 24, wherein said compound has the following structure:



n = 1 to 3
X = O, NH, NR where R is lower alkyl
Y = optionally substituted aryl or heterocyclyl.

31. The method, according to claim 24, wherein said compound has the following structure:



n = 0 to 2
X = O, S, SO, SO_2, NH NR or $N(CH_2)_mCOOH$ where m is 0 or 2
Y = aryl or heterocyclyl substituted with $(CH_2)_mCOOH$ where m is 0 to 2.

32. The method, according to claim 22, wherein the patient is a human.

33. The method, according to claim 22, wherein said method is used to treat a condition selected from the group consisting of hypertension, angina, ischemia, arrhythmia, congestive heart failure, and cardiac insufficiency.